

PEDIATRIC PRECLINICAL TESTING PROGRAM (PPTP)

EXECUTIVE SUMMARY

The NCI-supported Pediatric Preclinical Testing Program (PPTP) is a comprehensive program to systematically evaluate new agents against childhood solid tumor and leukemia models. The PPTP is supported through an NCI research contract to St. Jude Children's Research Hospital (SJCRH) with Dr. Peter Houghton as the Principal Investigator. Testing occurs both at SJCRH and also at subcontract sites that have expertise in specific childhood cancers, including: Children's Hospital of Philadelphia (John Maris), Albert Einstein Medical Center (Richard Gorlick), Duke University (Henry Friedman), Children's Hospital of Los Angeles (Patrick Reynolds), and Children's Cancer Institute Australia (Richard Lock).

The primary goal of the PPTP is to identify new agents that have the potential for significant activity when clinically evaluated against selected childhood cancers. The program is based on a substantial body of data showing that appropriate childhood cancer preclinical *in vivo* models can recapitulate the antitumor activity of known effective agents and can prospectively identify novel agents subsequently shown to have clinical activity against specific cancers of children and adolescents.

The PPTP systematically tests approximately 12 agents or combinations of agents annually in *in vitro* and *in vivo* preclinical models of common childhood cancers. The PPTP seeks to test these agents near the time that they are entering phase 1 evaluation in adults with cancer and prior to their possible initial evaluation in children. Pharmacokinetic studies are performed to determine the systemic drug exposures associated with antitumor activity, which allows comparison between the drug exposures required for activity in the childhood cancer preclinical models and those achievable in humans. When appropriate for molecularly targeted agents, the degree of target modulation associated with antitumor activity is evaluated.

To facilitate interactions between pharmaceutical sponsors and the PPTP, NCI developed model material transfer agreements (MTAs) in collaboration with pharmaceutical sponsors and academic research centers. The provisions included in the model MTAs have been accepted by all of the PPTP institutions.

By facilitating development of a more reliable pediatric new agent prioritization process, the PPTP contributes to the goal of identifying more effective treatments for children with cancer.

Additional information about the PPTP can be obtained from the PPTP Project Officer:

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RATIONALE FOR THE PEDIATRIC PRECLINICAL TESTING PROGRAM (PPTP)

Scores of new agents are in development as cancer therapeutics. Only a fraction of these new agents can be systematically evaluated in children, largely because of the limited number of children eligible for early phase clinical trials. How can childhood cancer researchers select from among all potential candidate agents those that should be moved into clinical evaluation in children? This selection process is critical to future progress in curing more children diagnosed with cancer, as selecting effective agents for clinical evaluation makes progress likely, while selecting ineffective agents almost certainly precludes progress.

The PPTP is necessary in part because current knowledge of the biology of childhood cancers is insufficient to make *a priori* valid predictions about the clinical relevance to childhood cancers of new agents that target widely expressed cellular components (e.g. microtubules, kinesins, topoisomerases, proteasomes, hsp90, etc.) and new agents that target broadly active signaling pathways (e.g., MAP kinase, AKT, apoptosis, and farnesylation-dependent pathways). A molecularly characterized preclinical panel is also a valuable resource for testing agents directed against tumor specific targets (e.g., oncogenic fusion proteins).

The PPTP builds upon research by Houghton and colleagues demonstrating the ability of preclinical testing using rhabdomyosarcoma and neuroblastoma xenografts to predict for activity of new agents in children with these cancers.¹⁻⁷ For example, as summarized in the table below, the activity of standard agents against rhabdomyosarcoma is mirrored by their level of activity in xenograft lines.¹

Table 1
Sensitivity of rhabdomyosarcoma and colon adenocarcinoma xenografts to conventional cytotoxic agents

Agent/tumour type	Objective response rate (%) in the model	Objective response rate (%) in the clinic
<i>Rhabdomyosarcoma</i> ^a		
Vincristine	78	59
Cyclophosphamide	44	54
Actinomycin D	11	24
Doxorubicin	19	31
<i>Colon carcinoma</i>		
Vincristine	0	<10
Cyclophosphamide	0	<10
Actinomycin D	0	<10
Doxorubicin	0	<10
5-fluorouracil	17	15-20
Methyl CCNU	17	15-20

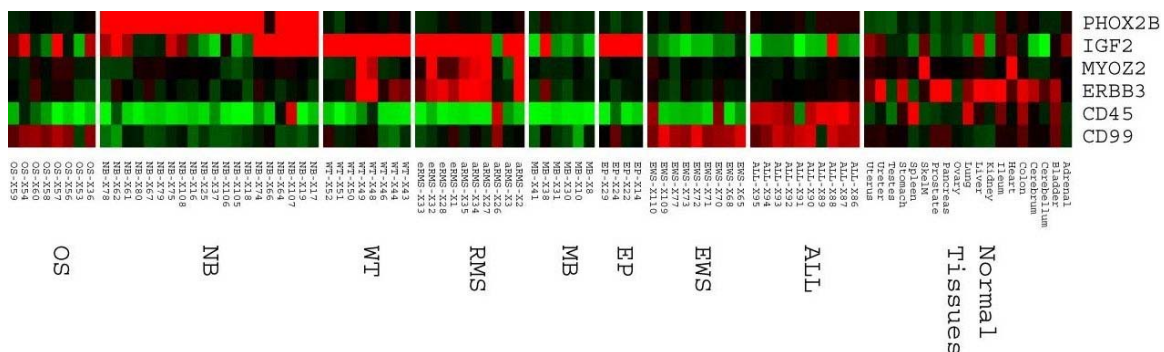
Subsequent work by Dr. Houghton in xenograft lines identified topoisomerase 1 inhibitors as active agents against rhabdomyosarcoma and neuroblastoma xenograft lines, a finding that was recapitulated when these agents were studied in the clinic against these diagnoses.²⁻⁵ Similarly, Lock and colleagues have developed data indicating that NOD/SCID models of childhood acute lymphoblastic leukemia (ALL) provide an accurate representation of the human disease, both in terms of biological characteristics and in terms of response to therapy.^{8,9} The PPTP is designed to extend these observations to other childhood cancer types and to a broader spectrum of anticancer agents.

MOLECULAR CHARACTERIZATION OF THE PPTP XENOGRRAFT AND CELL LINES

The PPTP childhood tumor xenograft models are being characterized by gene expression arrays (cDNA and Affymetrix) as well as by tissue arrays (prepared by Dr. Stephen Hewitt, NCI). These studies were initiated as part of the NCI/CTEP Pediatric Oncology Preclinical Protein-Tissue Array Project (POPP-TAP) initiative and are continuing in conjunction with the PPTP. Expression profiles from the cDNA arrays (performed by Javed Khan, NCI) and the Affymetrix arrays (performed at SJCRH) will be publicly available.

Results from gene expression studies will be informative as to whether specific tumors have characteristics of their tumors of origin (i.e. clustering with the appropriate clinical histology). Initial results from the POPP-TAP initiative indicate that xenograft lines for neuroblastoma, Ewing sarcoma, and rhabdomyosarcoma maintain the characteristic expression patterns of primary tumors with these diagnoses.¹⁰

The gene expression profiles may also be useful in evaluating the expression of potential therapeutic targets in specific xenograft and cell lines and in identifying associations between expression patterns and agent activity. As an example, the figure below demonstrates high level expression of insulin-like growth factor 2 (IGF2) for rhabdomyosarcoma and Wilms tumor lines, as well as the expected expression of PHOX2B (a homeobox transcription factor that functions in the differentiation of the sympatho-adrenal lineage) in neuroblastoma lines.



SNP analysis using the Affymetrix GeneChip Human Mapping array have been performed at SJCRH as a quality control measure and for use in characterizing the PPTP lines for regions of LOH and for chromosome copy number abnormalities.¹¹⁻¹³ Copy number abnormalities are being confirmed using oligonucleotide array comparative genomic hybridization (CGH).¹⁴

TESTING AGENTS THROUGH THE PPTP

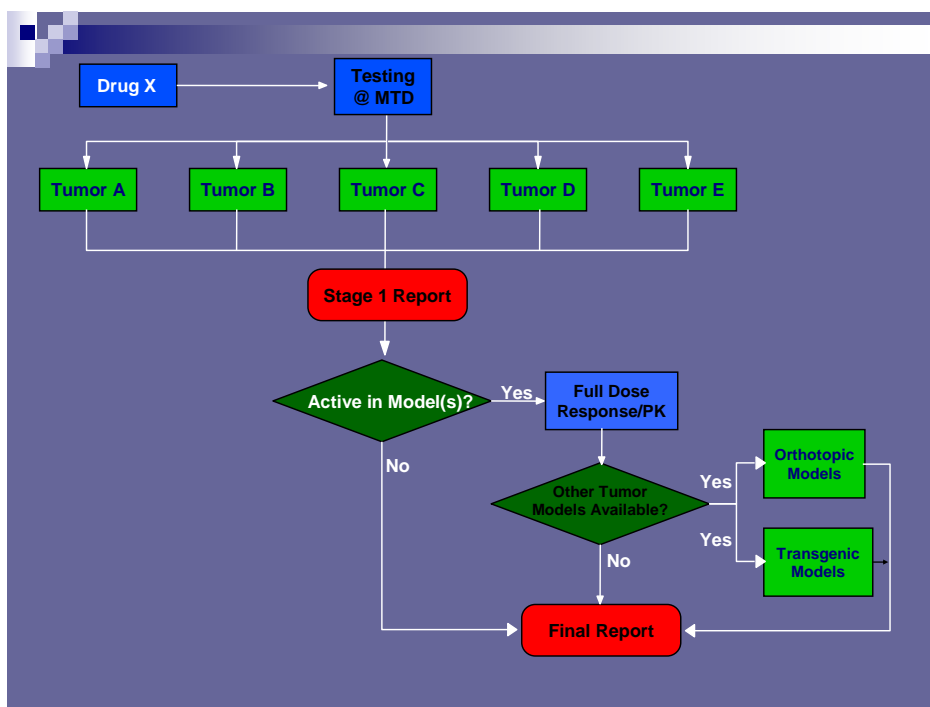
Several standard chemotherapy agents have been tested through the PPTP during its first year of operations in order to calibrate the PPTP tumor panels using agents of known clinical activity for specific tumor types. Two standard agents that have clinical utility against childhood cancer, cyclophosphamide and vincristine, were both identified as highly active in the PPTP screen.

New agents are ideally tested by the PPTP near the time that they are entering phase 1 evaluation in adults with cancer and prior to their possible initial evaluation in children. For both new agents and standard agents that show antitumor activity against PPTP childhood cancer models, pharmacokinetic studies are performed to determine the serum drug levels and systemic drug exposures associated with antitumor activity. For selected molecularly targeted agents, the PPTP evaluates whether target inhibition/modulation is achieved by the agent under the test conditions and whether this modulation is associated with antitumor activity. Results from the preclinical testing program will be correlated with the clinical activity and the pharmacokinetic profile of the tested agents in children to assess the predictive capabilities of the PPTP's childhood cancer panels and the animal models.

Testing for different tumor panels occurs both at SJCRH and also at subcontract sites that have expertise in specific childhood cancers as shown in the table below:

Site	Tumor Types Tested
St. Jude Children's Research Hospital	Rhabdomyosarcoma, Ewing sarcoma, Wilms tumor, Rhaboid tumor, Medulloblastoma, Ependymoma
Children's Hospital of Philadelphia	Neuroblastoma
Children's Cancer Institute Australia	Acute lymphoblastic leukemia
Duke University	High-grade gliomas
Albert Einstein Medical Center	Osteosarcoma
Children's Hospital of Los Angeles	<i>In vitro</i> panel

The operational schema for the PPTP shown in the figure below was developed following several meetings between CTEP/NCI and interested childhood cancer investigators.¹⁵



Stage 1 Testing: The agent is tested at its Maximum Tolerated Dose (MTD) in test animals to identify those agents that have significant antitumor activity against one or more of the PPTP's preclinical models. Agents entering Stage 1 testing are evaluated against multiple tumor panels, each panel representing a specific histotype and encompassing some of the genetic diversity of the disease. A full listing of the xenograft lines included in the PPTP's *in vivo* tumor panels is provided in Table 1. The PPTP has established panels for Stage 1 testing for sarcomas [rhabdomyosarcoma (n=6), Ewing sarcoma (n=5), and osteosarcoma (n=6)], neuroblastoma (n=6), acute lymphoblastic leukemia (n=8), glioblastoma (n=4), ependymoma (n=2), medulloblastoma (n=4), Wilms tumor (n=3), and rhabdoid tumor (n=3). Thus, each agent is evaluated in Stage 1 against 47 tumor models to determine the agent's level and spectrum of activity when it is administered at its MTD.

Stage 2 Testing: Those agents that demonstrate sufficient activity (either broad-spectrum or histotype specific) in Stage 1 testing are considered for Stage 2 testing. Detailed plans for Stage 2 testing are prepared following a comprehensive evaluation of the Stage 1 results by NCI, PPTP researchers, and the pharmaceutical sponsor for the agent. Additional drug supply is requested from the sponsor for the studies to which both parties agree. A key component of Stage 2 testing is determining dose response relationships using tumor models in which activity was observed in Stage 1. Stage 2 testing generally includes detailed pharmacokinetic and pharmacodynamic studies to establish the relationship between systemic exposure and antitumor activity. When appropriate for molecularly targeted agents, the degree of target modulation associated with antitumor activity is evaluated. Stage 2 testing may also include evaluation in appropriate secondary models (e.g., orthotopically implanted rhabdomyosarcoma and glioblastoma, and disseminated models of neuroblastoma) to confirm or refute results obtained using subcutaneous tumors. In addition, the

PPTP has access to selected genetically engineered mouse models that may be utilized when relevant during Stage 2 testing.

***In Vitro* Testing:** Selected agents are screened against a panel of 23 cell lines. The cell lines, representing each of the tumor types in the *in vivo* screening panels, are listed in Table 2. Testing is done in the laboratory of Dr. Patrick Reynolds using the DIMSCAN methodology developed in his laboratory. DIMSCAN is a semi-automatic digital image microscopy system for measuring relative cell numbers in tissue culture plates. Cytotoxicity assays measured by DIMSCAN using fluorescein diacetate, a dye accumulating selectively in viable cells, can achieve a 4 log dynamic range at 4 to 7 days, and correlate with colony forming assays. In selected cases, only following agreement with the supplier of the agent, combination studies can be undertaken to determine drug interactions that may be synergistic or antagonistic.

Drug supply and distribution: Sufficient agent is initially supplied to the PPTP to complete Stage 1 testing. Depending upon the results of the Stage 1 testing, a plan for Stage 2 testing is developed and the drug supply required for these additional studies is requested. For Stage 1 testing agents are tested at their MTD. Assuming the average test animal is .02 kg, then the total approximate drug requirement for phase 1 testing can be calculated as the product of the first 6 items in the table below, which provides the total drug requirement for an agent for which 1 mg/kg was the total dose per course and for which two courses were administered.

Dose per course (mg/kg)	1
# Lines	47
# Animals/Line	10
# Courses	2
Animal Weight (kg)	0.02
Dispensing/Reconstitution Factor	1.5 - 2
Drug Required (mg) per 1 mg/kg per course dose	28.2 - 37.6

Agents obtained from pharmaceutical sponsors are supplied to the PPTP Operations Center at SJCRH, which then distributes agents in a blinded fashion to sites for testing. Complete instructions for drug storage, formulation and administration are provided to sites by the PPTP Operations Center.

SUBMISSION/SELECTION OF AGENTS FOR EVALUATION THROUGH THE PPTP

Agents are selected for PPTP evaluation by the Project Officer, who is advised by the NCI Pediatric Drug Development Group (PedDDG). The PedDDG includes representation from the Investigational Drug Branch (CTEP), the Clinical Investigations Branch (CTEP), the Regulatory Affairs Branch (CTEP), the Developmental Therapeutics Program, and the Pediatric Oncology Branch. Its expertise encompasses preclinical drug development, early phase adult cancer drug development, regulatory and intellectual property issues related to preclinical testing, and pediatric oncology drug development. The PedDDG advises the PPTP Project Officer on all aspects of PPTP performance, including:

- Technical issues related to *in vitro* and *in vivo* testing,
- Regulatory and intellectual property issues related to obtaining new agents for testing,
- Identification of candidate agents for the PPTP to consider for testing, and
- Prioritization of agents for PPTP testing.

Criteria for bringing new agents forward for PPTP testing include:

- Likely availability of the agent for clinical testing in children within 12-24 months,
- Relevance of the agent's target to childhood cancers,
- Lack of prior evaluation of the agent's target by the PPTP, and
- Availability of sufficient quantity of the agent for testing across the entire PPTP panel.

Most agents selected for testing will have undergone considerable prior testing against adult preclinical cancer models. For these agents, information concerning drug formulation and optimal schedule/dosing must be made available to the PPTP. Pharmaceutical companies and cancer researchers wishing to nominate an agent(s) for evaluation by the PPTP should contact the NCI Project Officer. For agents that pharmaceutical companies wish to propose for PPTP testing, confidentiality agreements are prepared as necessary to allow provision of adequate information to NCI to allow a decision to be made about the appropriateness of evaluating the agent through the PPTP.

MATERIAL TRANSFER AGREEMENTS AND INTELLECTUAL PROPERTY PROVISIONS AND DISSEMINATION OF PPTP TEST RESULTS

Model Material Transfer Agreements (MTA) have been developed by NCI in collaboration with pharmaceutical sponsors and academic research centers. The provisions included in the model MTAs have been accepted by all of the PPTP institutions. NCI uses the model MTA to execute MTAs with those pharmaceutical companies providing agents for testing. NCI then executes MTAs with each of the PPTP institutions to allow provision of agents to the institutions for testing.

The primary objective of the PPTP is to develop preclinical data that will be useful to childhood cancer researchers in prioritizing new agents for clinical evaluation. Hence, it is essential that these data be made available to researchers in an expeditious manner. The PPTP's primary mechanisms for disseminating information is through peer-reviewed scientific journals and through presentation of data and results at academic symposia or similar professional meetings. As specified in the model MTA, such manuscripts may be submitted for publication only after the pharmaceutical sponsor has had forty-five days to review the proposed disclosure to determine if it includes any confidential or patentable information. Abstracts must be provided to the pharmaceutical sponsor in sufficient time to allow at least seven days to review any planned submission. In order to expedite publication of test results, the PPTP utilizes a manuscript template to facilitate rapid development of manuscripts upon completion of testing and analysis of test results.

SUMMARY

The PPTP is the first comprehensive effort to systematically test anticancer agents against a broad range of childhood cancer preclinical models, and it complements similar efforts for adult cancers that are supported by NCI and by pharmaceutical companies. The NCI-supported PPTP is a comprehensive program to systematically evaluate new agents against childhood solid tumor and leukemia models. The program is based on a substantial body of data showing that appropriate childhood cancer preclinical *in vivo* models can recapitulate the antitumor activity of known effective agents and can prospectively identify novel agents that are subsequently shown to have clinical activity against specific cancers of children and adolescents. By facilitating development of a more reliable pediatric new agent prioritization process, the PPTP contributes to the goal of identifying more effective treatments for children with cancer.

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Table 1. Pediatric Preclinical Testing Program *in Vivo* Panel

NAME	DIAGNOSIS	PANEL	STATUS	PROPERTIES
WT-10	Wilms tumor	Primary	Diagnosis	Favorable Histology
WT-11	Wilms tumor	Primary	Diagnosis	Favorable Histology
WT-13	Wilms tumor	Primary	Diagnosis	Diffuse Anaplastic
WT-5	Wilms tumor	Secondary		Nuclear Unrest
BT-29	Rhabdoid tumor	Primary	Diagnosis	
WT-14	Rhabdoid tumor	Primary	Relapse	
WT-16	Rhabdoid tumor	Primary	Relapse	
WT-12	Rhabdoid tumor	Secondary	Diagnosis	
CHLA258*	Ewing sarcoma	Primary		
EW5	Ewing sarcoma	Primary	Diagnosis	
EW8	Ewing sarcoma	Primary	Diagnosis	
SK-NEP-1**	Ewing sarcoma	Primary	Relapse	
TC-71	Ewing sarcoma	Primary	Relapse	
Rh10	Rhabdomyosarcoma	Primary	Relapse	Alveolar
Rh18*	Rhabdomyosarcoma	Primary	Diagnosis	Embryonal
Rh28	Rhabdomyosarcoma	Primary	Diagnosis	Alveolar
Rh30*	Rhabdomyosarcoma	Primary	Diagnosis	Alveolar
Rh30R	Rhabdomyosarcoma	Primary	Relapse	Alveolar
Rh41*	Rhabdomyosarcoma	Primary	Relapse	Alveolar
Rh36	Rhabdomyosarcoma	Secondary	Relapse	Embryonal
Rh65	Rhabdomyosarcoma	Secondary	Relapse	Alveolar
OS-1	Osteosarcoma	Primary	Diagnosis	
OS-2	Osteosarcoma	Primary	Diagnosis	
OS-9	Osteosarcoma	Primary		
OS-17	Osteosarcoma	Primary	Diagnosis	
OS-31	Osteosarcoma	Primary		
OS-33	Osteosarcoma	Primary		
OS160	Osteosarcoma	Secondary	Def. Surg	
OS-29	Osteosarcoma	Secondary		
BT-36	Ependymoma	Primary	Diagnosis	
BT-41	Ependymoma	Primary	Relapse	
BT-44	Ependymoma	Secondary		
BT-54	Ependymoma	Secondary	Relapse	
BT-28	Medulloblastoma	Primary	Diagnosis	
BT-45	Medulloblastoma	Primary	Diagnosis	
BT-46	Medulloblastoma	Primary	Diagnosis	
BT-50	Medulloblastoma	Primary	Diagnosis	
D456	Glioblastoma	Primary	Diagnosis	
D645	Glioblastoma	Primary	Diagnosis	
SJ-BT39	Glioblastoma	Primary	Relapse	
SJ-GBM2*	Glioblastoma	Primary	Relapse	
D212	Glioblastoma	Secondary	Diagnosis	
SJ-BT56	Glioblastoma	Secondary	Relapse	

NAME	DIAGNOSIS	PANEL	STATUS	PROPERTIES
CHLA-79	Neuroblastoma	Primary	Relapse	Non MycN amp
NB-1643*	Neuroblastoma	Primary	Diagnosis	MycN amp
NB-1691	Neuroblastoma	Primary	Relapse	MycN amp
NB-1771	Neuroblastoma	Primary	Diagnosis	MycN amp
NB-EBc1*	Neuroblastoma	Primary	Relapse	Non MycN amp
NB-SD	Neuroblastoma	Primary	Relapse	MycN amp
NB-1382	Neuroblastoma	Secondary	Relapse	MycN amp
SK-N-AS	Neuroblastoma	Secondary	Relapse	Non MycN amp
ALL-2	ALL	Primary	Relapse	B-precursor
ALL-3	ALL	Primary	Diagnosis	B-precursor
ALL-4	ALL	Primary	Diagnosis	B-precursor (Ph+)
ALL-7	ALL	Primary	Diagnosis	B-precursor
ALL-8	ALL	Primary	Relapse	T-cell ALL
ALL-16	ALL	Primary	Diagnosis	T-cell ALL
ALL-17	ALL	Primary	Diagnosis	B-precursor
ALL-19	ALL	Primary	Relapse	B-precursor
ALL-10	ALL	Secondary	Diagnosis	B-precursor
ALL-11	ALL	Secondary	Diagnosis	B-precursor

*Line also in *in vitro* panel

**Previously considered anaplastic Wilms tumor, but confirmed to be Ewing family tumor based on EWS-ETS gene fusion transcripts

Table 2: Pediatric Preclinical Testing Program *in Vitro* Panel:

Name	Diagnosis	Panel
RD	Rhabdomyosarcoma	Primary
Rh41*	Rhabdomyosarcoma	Primary
Rh18*	Rhabdomyosarcoma	Primary
Rh30*	Rhabdomyosarcoma	Primary
BT-12	Rhabdoid	Primary
TC-71	Ewing sarcoma	Primary
CHLA-9	Ewing sarcoma	Primary
CHLA-10	Ewing sarcoma	Primary
CHLA-258	Ewing sarcoma	Primary
CHLA-266	PNET Brain	Primary
SJ-GBM2*	Glioblastoma	Primary
NB-1643*	Neuroblastoma	Primary
NB-EBc1*	Neuroblastoma	Primary
CHLA-90	Neuroblastoma	Primary
CHLA-136	Neuroblastoma	Primary
NALM-6	Pre-B cell ALL	Primary
COG-LL-317	T-cell ALL	Primary
RS4;11	Pre-B cell ALL	Primary
MOLT-4	T-cell ALL	Primary
CCRF-CEM	T-cell ALL	Primary
Kasumi-1	AML	Primary
Karpas-299	Anaplastic Large Cell Lymphoma	Primary
Ramos	Burkitt's Lymphoma	Primary
CHLA-122	Neuroblastoma	Secondary
CHLA-119	Neuroblastoma	Secondary
SUDHL-1	Anaplastic Large Cell Lymphoma	Secondary
MV-4-11	AML	Secondary

*Line also in *in vivo* panel.

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